EXHIBIT 7

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it is -- were your words commonly seen in all patients?

Q. Common to.

A. Common to all patients? Well, certainly I wouldn't know how to parse that.

Is that what he asked?

Q. I'm telling you what I asked you. So here's my next question to you.

A. I'm sorry. Can we go back to that question or is that okay?

Q. Have you answered that question?

A. I would say that malabsorption is sufficiently vague so as to not be a great way to be noted as a universal or common to all patients with olmesartan.

Q. So then am I correct that in your view, malabsorption is not a symptom that is required to diagnose sprue-like enteropathy?

A. So depending on how you consider malabsorption, but certainly

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fatty diarrhea, for example, not all patients with olmesartan enteropathy reported that. One can have severe injury of the small bowel, for example, due to olmesartan and still somehow, you know, retain the capacity to absorb fat.

And, you know, you could potentially have that patient also with iron deficiency anemia and one person might actually say that is malabsorption because they are malabsorbing iron; whereas, someone else might say, I consider malabsorption to be specifically related to fat malabsorption and, if there's no diarrhea, I wouldn't call that malabsorption.

So I think it's not a very helpful term when trying to characterize a clinical phenotype --

Q. How about villous atrophy; is villous atrophy a symptom or condition that is common to all who have been diagnosed with sprue-like enteropathy?

A. I'm still getting hung up on

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"common to all." I apologize, but it doesn't seem to make sense.

Q. That's fine. To diagnose someone who you believe has sprue-like enteropathy, must that individual present with villous atrophy?

A. I think that the literature has borne out that villous atrophy is not always a feature in olmesartan enteropathy; and, frankly, in real life, many patients with diarrhea don't end up even getting a duodenal biopsy.

If I could refer you to the study on my reliance list where I'm the lead author published in Gastrointestinal Endoscopy that I made passing reference to previously on sex and racial disparities in the diagnosis of celiac disease, in that study, we looked at a national endoscopy database, a clinical outcomes research initiative national endoscopy database, and we found that a large proportion of individuals undergoing endoscopy for a number of

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clinical features suggestive of celiac disease, including diarrhea, iron deficiency, anemia, weight loss, who underwent endoscopy nevertheless did not have a small intestinal biopsy performed. And we thought that was remarkable and worth publishing.

And the take-away is that it appears that, in the community, people who have symptoms suggestive of malabsorption or symptoms that are certainly compatible with olmesartan enteropathy, not only might they undergo an upper endoscopy, it's possible some of them get an upper endoscopy and don't even have a biopsy.

And so I would be hesitant to say that villous atrophy is quote common to all patients who have olmesartan enteropathy, when we know that at least in an analogous disease, a lot of patients never get biopsied.

Q. Well, I guess then the question becomes, among those who in fact

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have had the endoscopy, is there a finding of villous atrophy?

A. It has certainly been reported and indeed in the Rubio-Tapia initial case series, they all had villous atrophy, but as the literature has subsequently borne out, it appears that lesser degrees of villous architectural distortion or perturbation can be present.

And I think that makes sense. I'm honestly not very surprised that that was borne out based on, again, analogizing to celiac disease. Turns out that while villous atrophy is present in celiac disease, there are people who get biopsied and, due to a number of circumstances, they don't have villous atrophy in that biopsy specimen.

That could be due to the fact that villous atrophy in celiac disease is patchy and that might not be -- that might -- rather, that might be the case in olmesartan enteropathy. It

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could be that it was just missed in terms of location.

Certainly one thing we've learned from celiac disease is, the small intestine does not have to look abnormal to the naked eye on endoscopy in order for a patient to have villous atrophy, and I think that's one reason for the underbiopsy rates in celiac disease. People might be assuming that if it looks okay to the naked eye, it's not worth taking a biopsy.

But even among those who do get a biopsy, there is abundant literature that shows us that celiac disease at least can be missed if an insufficient number of specimens are submitted, and there's also been a number of case reports of findings convincing for the clinical phenotype of olmesartan enteropathy in which the villous architecture was actually above what we consider normal, otherwise known as a villous height to crypt depth ratio was

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seen as normal.

Q. I was asking you about features, features that are common in the diagnosis of sprue-like enteropathy. And you told me no as to malabsorption --

A. I'm sorry. I don't think that -- I believe --

MR. SLATER: Yeah, I object to the form of the question.

You can answer.

THE WITNESS: I don't think I said, no, that malabsorption -- in response to the question of malabsorption was a feature.

I just think that malabsorption is a somewhat ill-defined entity and so I'd be hesitant to say that it's common or rare within olmesartan enteropathy simply because it can be defined variously.

BY MR. MURPHY:

Q. And the same with regard to villous atrophy.

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MR. SLATER: Objection.

THE WITNESS: Villous atrophy has more objective definitions than malabsorption. While interobserver agreement between pathologists is not perfect with regard to the presence of villous atrophy and I certainly have had the experience where patients with celiac disease have a biopsy that's interpreted differently by two different pathologists, there are more agreed-upon parameters for villous atrophy than there are, for example, for malabsorption.

And so, for example, if a doctor is referring a patient to me and over the phone he says that this patient has villous atrophy, I'm pretty sure I know what that doctor means; whereas, if they say malabsorption, I sort of chalk that up to a, well, that could

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mean a lot of different things.
In medicine, we have such terms and I tell my trainees to be careful when using terms that are defined variously. Lethargic is another -- is another example. Lethargic could mean somewhat sleepy because of insufficient amount of sleep. Lethargic could mean substantial mental status change and we need to work this up acutely because we're worried there's something going on.
Malabsorption's not quite that bad, but it's something that I think we need to exercise some caution on, particularly when trying to pin a clinical entity and label with malabsorption.
BY MR. MURPHY:
Q. How about diarrhea; is diarrhea a feature that must be seen in order to diagnose one as having olmesartan-associated enteropathy?

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A. I don't think it must be present. I think that diarrhea is commonly reported in people who turn out to have olmesartan enteropathy.
Not to get too technical, there are definitions of diarrhea and there is a little bit of subjectivity to that, but I think the literature's borne out that you don't need to have diarrhea to have olmesartan enteropathy.
I believe you could have potentially constipation. I think there's potentially an explanation for that. If you have, you know, a -- an injured gut epithelium, that could potentially affect the enteric nervous system and that could actually paradoxically induce constipation. Just like, you know, some people when they're undergoing stress gain weight and some people when they're undergoing stress lose weight, there does appear to be this varied clinical presentation.
But I would say that

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diarrhea is a common feature in patients with olmesartan enteropathy.
Q. With regard to constipation, did any of the -- those who were participants in the Rubio-Tapia case series present with constipation?
A. Rubio-Tapia's case series was somewhat narrowly defined. If you look at their inclusion criteria, patients were considered for inclusion of the study if they had chronic diarrhea, so it's very possible that Dr. Rubio-Tapia and colleagues were encountering other people, patients, who had olmesartan enteropathy, but they just didn't make it into this series, because they predefined who made it in.
So while it is possible to have both chronic diarrhea and intermittent bouts of constipation, it appears based on my interpretation of this paper that they were limiting their case series to those with chronic diarrhea.

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Q. And that that limited group of folks that they looked at were the ones that they relied upon in reaching the conclusion that they reached in their paper regarding an association. Right?
A. Well, what they did is, when they were first presenting this case series, they chose a relatively narrow clinical phenotype, so as to describe the first patients in the medical literature aside from an earlier, almost parenthetical, mention in a paper about collagenous sprue a few years before.
And so while I can't get inside their heads, I believe that they were -- that they were targeting a homogeneous or relatively homogeneous clinical phenotype for this first description.
Q. Let me direct you to your report and in particular page 5.
MR. SLATER: I just want to -- I'm not suggesting that you do this. I just want to make it

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clear that he could continue to list articles that either --
MR. MURPHY: Is that what you're telling him to do?
MR. SLATER: No, I'm not and I can even say it outside -- I just want to make a record that you went to a new subject after you started to question about what articles talk about causation. I just want to make it clear that he wasn't asked are there any more you want to list.
If you want to move to another subject, it's fine. I just don't want the record to seem as if he finished.
MR. MURPHY: Oh, well, I thought you had. I thought that I had the four articles that spoke strongly and then we have Rubio-Tapia --
THE WITNESS: That was not what I meant to convey. I think

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we got --
MR. MURPHY: My apologies. I would like for you to exhaust your list of articles that reached the conclusion that olmesartan causes sprue-like enteropathy.
THE WITNESS: Can you read to me --
MR. MURPHY: Thank you, Adam.
THE WITNESS: Can you read to me the ones that I had mentioned already?
MR. MURPHY: You had Talley, Lebwohl and --
THE WITNESS: Ludvigsson.
MR. MURPHY: -- correct -- Marild and Lagana, Braunstein.
THE WITNESS: I believe I mentioned some others. I mentioned Rubio-Tapia --
BY MR. MURPHY:
Q. Right. I'm saying before we got to Rubio --

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A. I went on and listed Basson at some length, I think --
Q. You listed Basson over here on the right.
A. Why don't I take a look. If you really want every one of them, I must say it's becoming increasingly taken for granted, so it's often listed in the title. Indeed, if you look for the expression "olmesartan-induced enteropathy," that's popping up left and right in PubMed.
Q. Just give me the list of the articles.
A. Why don't I take a look. DeGaetani, did I mention that one yet?
MR. SLATER: Not yet.
THE WITNESS: Would you like me to go to the specific instance of where causation was either explicitly mentioned or at least strongly implied?
MR. MURPHY: I'm just asking

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for the titles of the articles.
THE WITNESS: Okay.
(Pause.)
THE WITNESS: Aziz and colleagues interpret the initial Rubio-Tapia paper as indicating causation.
(Pause.)
THE WITNESS: I would argue that causation is strongly implied in the review article by Nina Burbure and colleagues, B-U-R-B-U-R-E.
BY MR. MURPHY:
Q. And you said, there, it's implied.
A. Strongly implied.
Q. Strongly implied.
A. In the case described by de Fonseka, the title is "A case of olmesartan-induced enteropathy."
I should also point out an item that's in my report, a table of causes of villous atrophy from the

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physician reference uptodate.com, I can reference my report to where that is. That is peer reviewed. It's not in PubMed and it's a subscription service. It's on page 9 of my report. Olmesartan is listed as a cause of small intestinal villous atrophy.

Q. That's not an article, is it? That's just a chart.

MR. SLATER: Up-to-Date?

THE WITNESS: Well, I would point out that it came from an article in Up-to-Date. I did give the caveat that it's not in PubMed. It might not be widely available to the general or scientific public because it is subscription. It's a subscription service that is widely used by physicians, certainly not universally used, but it is a peer-reviewed article.

MR. MURPHY: And that's what I'm trying to understand.

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BY MR. MURPHY:

Q. And the title of the article?

A. I don't have the title of that article.

Q. Okay. All right.

A. On my person.

Q. We can move on.

(Pause.)

THE WITNESS: Marietta, Cartee, Rishi, and Murray, "Drug-induced enteropathy."

Marietta and colleagues, "Immunopathogenesis of olmesartan-associated enteropathy," Alimentary Pharmacology and Therapeutics, 2015. Marthey and colleagues, "Olmesartan-associated enteropathy: results of a national survey," Alimentary Pharmacology and Therapeutics, 2014: "In conclusion, this study shows that olmesartan causes severe and

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potentially life-threatening enteropathy with or without villous atrophy."

Pardon me. Are we limiting this to the peer-reviewed literature or possibly internal Daiichi documents?

MR. MURPHY: Articles. I asked you for the articles.

THE WITNESS: Just making sure.

MR. MURPHY: Okay.

THE WITNESS: Philip and colleagues, "Spectrum of Drug-induced Chronic Diarrhea," Journal of Clinical Gastroenterology.

(Pause.)

THE WITNESS: Uehara and colleagues, "Olmesartan-induced Enteropathy Manifesting as Wernicke-Korsakoff Syndrome."

BY MR. MURPHY:

Q. Before you identify the next

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article, I want to be sure that I remember what you said earlier about Uehara. That was one of the articles of which you had not been aware at the time you generated your report; correct?

A. I believe that either came out later or only made its way to my attention after I finished my report.

Q. Okay. I'm sorry. Go ahead.

A. Theophile and colleagues, "Five cases of sprue-like enteropathy in patients treated by olmesartan."

I should look at my supplementary reliance list to make sure that I'm being complete. I'm not sure if everything in my binder here was on this list, but based on the Uehara article, that suggests that perhaps it is.

Did I mention Philip and colleagues, "Spectrum of Drug-induced Chronic Diarrhea"?

Q. You did.

A. Thank you.

How about Hammoudi and

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colleagues, "Olmesartan-induced enteropathy associated with cutaneous lesions"?

Q. What number is that on your --

A. It's number 14 on my supplemental reliance list, note the use of the word "induced."

Hartranft and colleagues, "'Triple Phase' Budesonide Capsules for the Treatment of Olmesartan-Induced Enteropathy," Annals of Pharmacotherapeutics, 2013.

Q. I'm sorry. What number is that?

A. Number 18.

Those are the ones that I could find on a first pass. It's possible there are others. As I mentioned, this is a notion that's now even taken for granted in the medical literature, so it's not often headlined in the conclusion of each article, but it's clear that either these articles

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either conclude or take for granted or imply or strongly -- or strongly imply causation.

How are we doing for time?

MR. MURPHY: We're doing fine.

Your last response gives me some pause, because one of the things I understood you to say was that they imply, and my question was conclusion that it does cause. That was the import of my question.

But it is what it is at this point. We won't go back through. I'm not going to ask you to modify your answer. I gave the question. You provided the answer.

MR. SLATER: That's not a question. So he's just --

MR. MURPHY: I'm just trying to make sure you understand my view of it.

We are about 12:30. Are we

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at a good time for a break? Do you want to keep going forward?

THE WITNESS: I think it's a good time for a break.

(A luncheon recess was taken from 12:25 p.m. to 1:11 p.m.)

THE WITNESS: Before we get started, I did find another couple of articles in the literature about causation, regarding conclusion of causation.

MR. MURPHY: Okay.

THE WITNESS: One is by Cartee.

BY MR. MURPHY:

Q. Cartee, Murray?

A. Yeah. The other is by Greywoode and colleagues, "Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study," Mayo Clinic Proceedings, 2014.

Q. I want to clear up a couple of things before we move on to the next

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area. Earlier, before we broke, I had asked you a couple of questions about common features. Do you recall that? Common features associated with folks who have been on olmesartan and are believed to have olmesartan-associated enteropathy.

A. I remember that.

Q. You remember that. Okay.

Have you ever seen a case of someone who has taken olmesartan, complained of GI symptoms, and yourself concluded that olmesartan was not the cause of the GI symptoms in question?

A. Do you mean in the literature or in my own clinical practice?

Q. In your own clinical practice.

A. I'm trying to think if I can come up with a specific instance, but the truth is, olmesartan is not a very popular medication in patients who come to see me, apart from those who are very

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ill from it, so I'm hesitant to recall a specific situation where someone came to me and I concluded olmesartan is not causing their symptoms.

I could imagine such a case, of course.

Q. You have no recollection of seeing such a case.

A. I can't think of a specific patient that comes to mind right now.

Q. That's fair. Have you seen such a case in the literature?

A. Well, it would be an odd type of case report to write. Usually people publish positive case reports after dechallenge, rechallenge.

I could imagine a situation where someone was taking olmesartan and ended up having a problem that was not related to olmesartan, but I don't think that that's the type of thing that people write up.

Q. Publish. So when there is -- when causation is not established or

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tied to an agent, that is not the type of thing that typically finds its way into an article; is that what you're saying?

A. Can you repeat that?

Q. Sure. When causation's not established, that is, when it's determined that the agent in question, here olmesartan, is not the cause of the GI symptoms reported upon, that is the type of thing that typically is not written up in an article.

A. It depends. It depends what the focus of the article is. For example, I think it would be worthwhile, and indeed we did such a study, where we wanted to really explore the degree to which olmesartan enteropathy cases published at the time of Rubio-Tapia paper represented the tip of the iceberg.

And so what we did is, we took a look at outpatients who had diarrhea and we did a case-control study and we at the time looked at a whole number of medications. We were really

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interested in better understanding the boundaries of olmesartan.

We really -- when Rubio-Tapia and colleagues published their case series, at the time, we were focusing on the sickest of the sick and what we wanted to know is, is this stuff causing diarrhea much more widely. And so we cast a very broad net and we looked at outpatients undergoing evaluation for diarrhea.

Now, that finding was -- in a word, it was null, it was negative, but that's very different from saying that this is a situation where I can find a specific patient that olmesartan's not causing that patient's diarrhea. I'd be hesitant to conclude that from that study design.

Q. So when you -- when the conclusion was null, what was that conclusion? So the null conclusion was what?

And by the way, while you're

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looking, this is reported in which article?

A. So I'm referring to the article by Greywoode and colleagues from Mayo Clinic's Proceedings.

The null finding refers to the hypothesis or question of whether, among outpatients undergoing evaluation for diarrhea, olmesartan is a common culprit.

Q. Understood.

A. It turns out that the great majority, about 99 percent of them, weren't taking olmesartan and so one thing that we didn't know at the outset of that study -- and this is the way research works, is one comes up with a study design and a hypothesis, but before you actually get a look at the data, we didn't really know how popular olmesartan was or unpopular it was -- so we found, unfortunately, that this exposure wasn't very common in either group, which really limited our ability to draw firm

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conclusions.
Q. And this is Greywoode.
A. Greywoode and colleagues, yes.
Q. Yet that is one of the papers that you cite as concluding that olmesartan causes sprue-like enteropathy; correct?
A. I listed that, correct, because we do indicate that causality has been established in that article. If you look at the last sentence of the conclusion, "Future studies should focus on the mechanisms by which olmesartan causes severe sprue-like enteropathy," et cetera, so this to me indicates this is a peer-reviewed research study that in its conclusion makes reference to the fact that olmesartan causes sprue-like enteropathy.
Q. So you believe that those authors were of that view that olmesartan causes sprue-like enteropathy.
A. Yes.

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Q. Okay.
A. I do. I'm one of those authors and I believe that olmesartan causes sprue-like enteropathy, as you know.
Q. At page 27 of your report, if I can direct you to your report, and particularly page 27 --
A. I'm on page 27.
Q. -- toward the end of the first full paragraph, you write, "Though case reports are generally low on the hierarchy of evidence when assessing for causality, evidence from a rechallenge is particularly strong."
That's what you write; correct?
A. That's what I write.
Q. And so you acknowledge that there is a hierarchy of causality evidence.
MR. SLATER: Just objection. You can answer.
THE WITNESS: There is a

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generally recognized hierarchy of study types, but that hierarchy is a generic hierarchy.
MR. MURPHY: Okay.
THE WITNESS: That hierarchy puts systematic reviews and meta-analyses at the very top, usually above what we typically see as the gold standard, the randomized controlled trial; and, indeed, it does put case reports and case series at the bottom.
That hierarchy, frankly, is much more useful when looking at efficacy of interventions and is, I would say, hardly relevant when specifically evaluating long-term, uncommon adverse events.
BY MR. MURPHY:
Q. So with regard to -- and I want to make sure we're clear on this -- this general hierarchy, randomized controlled trials are at the top --
A. Well, systematic reviews and

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meta-analyses of randomized trials are sometimes put on top of that because of the possibility that specific or individual RCTs can be fraught for various reasons; and so the rationale is, if you pool them, you can potentially diminish sources of bias in any individual ones.
That, though, is a generic hierarchy that I'd say is not particularly applicable to the issue at hand, which is, does this agent cause in the long term an adverse event.
Randomized trials don't last long enough to pick up adverse events and so to cite the hierarchy of evidence or to diminish the importance of case reports and case series is, I think, a diversion.
Q. Within this general hierarchy, cohort and case-control studies have a place, correct, in this hierarchy?
MR. SLATER: Objection.

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You can answer.
THE WITNESS: If you're referring to the generic hierarchy of evidence-based medicine as a movement, as a principle, cohort studies and case-control studies are in that pyramid, again, with randomized trials, possibly meta-analyses, at the very top and then case reports and case series further down at the bottom.
But I would -- I would emphasize that this is -- this is not well applicable to the issue at hand.
BY MR. MURPHY:
Q. And it's your view that the cohort or case-control studies simply don't last long enough to capture the development of the enteropathy?
A. I believe I said that randomized controlled trials don't last long enough --
Q. I know. I was asking

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whether you had the same criticism or view with regard to cohort and case-control studies.
A. Well, that would depend on the duration of follow-up. I'm fortunate to have a collaboration with Swedish epidemiologists in some of my research and, in Sweden, people can be followed from cradle to grave because of the nature of their healthcare system and record-keeping, and so you can do powerful cohort studies that follow people really over decades.
Randomized controlled trials, you can't really do that. It's just not affordable and totally impractical. And, indeed, evidence can be gleaned from cohort studies and case-control studies, even among -- with regard to long-term adverse effects, provided that those data sets available follow patients for long enough.
Q. Now, when I asked you for a list of articles that conclude that

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olmesartan causes sprue-like enteropathy and you gave me that list, were any of those case-control studies?
A. It would be helpful if you could read the list back to me. If you could do so, I can identify as you read them whether they were case-control studies.
Q. Talley?
A. No.
Q. Your paper with Ludvigsson?
A. Would that be the one with Marild as the first author?
Q. No. That's the third.
A. Oh, that was an editorial, so, no, it was not a case control study.
Q. Marild.
A. No. I believe that was a population-based cohort study; but before I answer definitively, that might have been case control, so I want to check.
Q. That's fair.
(Pause.)
THE WITNESS: Oh, in fact,

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this was a case-control study.
BY MR. MURPHY:
Q. Which one? Marild?
A. Marild, yeah.
Q. Lagana and Braunstein?
A. Who's the last author on that one? Is that me? I think that's me.
So Lagana and Braunstein, if you mean Lagana, Braunstein, Lebwohl, Green, "Angiotensin Receptor Blockers Other than Olmesartan Are not Associated With Histologic Evidence of Duodenitis," that was not a case-control study.
Q. DeGaetani?
A. That was not a case-control study.
Q. Aziz?
A. No.
Q. Burbure?
A. No.
MR. SLATER: You missed some from the early part of his list, just saying.

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BY MR. MURPHY:
Q. Did you say no as to Talley?
A. Talley, I said no. Talley, though, I should point --
Q. Please.
A. -- Talley was commenting on the result of a population-based cohort study; and while Talley's paper was not original research, I would argue that it was a prominently published opinion piece summarizing that research in a highly regarded and cited journal.
Q. How about de Fonseka?
A. No.
Q. Either of the Marietta papers?
A. The Marietta paper titled "Drug-Induced Enteropathy" was not a case-control study. The other Marietta paper, "Immunopathogenesis of olmesartan-associated enteropathy," while it did include a control population, it's not, as it's classically understood to be, a case-control study.

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Q. Marthey?
A. No.
Q. Philip and colleagues.
A. No.
Q. Basson.
A. Basson had controls, but this was not a case-control study. It was a cohort study.
Q. Uehara.
A. No.
Q. I think it's Theophile?
A. No.
Q. Hammoudi?
A. Did you say Hammoudi?
Q. It's number 14.
A. Thank you. No.
Q. Hartranft, number 18.
A. No.
Q. How about Aziz?
A. I think you asked me about that one already, hadn't you? And it's still not a case-control study.
Q. And how about Rubio-Tapia?
A. Rubio-Tapia and colleagues,

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"Severe Spruelike Enteropathy Associated with Olmesartan"? No, that was not a case-control study.
I believe there's one on my list, though, that you haven't mentioned, but maybe --
Q. Which -- you tell me. I thought I covered them all --
A. Greywoode?
Q. Okay. Greywoode.
A. Yeah, if I'm remembering accurately, when we resumed from the break, I mentioned two more and Greywoode was one of those two and the other was Cartee. Greywoode is a case-control study. Cartee is not.
Q. So Greywoode being a case-control study, anything in Greywoode suggest a statistically significant correlation between olmesartan and sprue-like enteropathy?
A. Well, certainly in the -- in the conclusion of our study, we make reference to the fact that olmesartan

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causes severe enteropathy; but in terms of the analysis, we actually did in that study -- there were no statistically significant associations found between olmesartan and diarrhea or sprue-like enteropathy.
Q. Okay.
A. I would note, though, as we do in our study, that we really didn't have that many people taking olmesartan which severely impacted our power.
If you look, for example, at table 1, if you add up the columns of olmesartan users among those undergoing EGD, which is esophagogastroduodenoscopy, and olmesartan users among those undergoing colonoscopy, you barely get a hundred patients.
We did not know that olmesartan was going to be so unpopular at the time that we designed this study, but at the end of the day, this is what we found among these individuals in their records.

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The reason that's relevant is that the fewer patients you have with regard to the exposure, the more limited one's power is and the wider one's confidence interval is.

And so, you know, as we acknowledge in our limitations section of the paper, it was also a relatively small prevalence of use of olmesartan, .7 percent to 1 percent among study patients, limiting the power of this analysis, as I say.

I would also point out the 95 percent confidence interval for olmesartan -- you can see in table 3, the odds ratio is calculated 1.99 and the 95 percent confidence interval overlaps with 1, which is the unity in terms of a signal being detected with regard to an association, and that's why the P value is 0.14, not statistically significant.

But if you look -- and this is really a direct consequence of having so few patients on olmesartan in the

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study -- that confidence interval is very wide. So it goes from .79, less than 1, protective, to 5.00, very strongly correlated or fivefold increased risk.

And so an interpretation or a common interpretation of a 95 percent confidence interval is that we can state with 95 percent confidence that the true association between olmesartan use and this kind of diarrhea is somewhere between .79 and fivefold increase compared to non-olmesartan users.

Q. Understood.

And P values -- again, P values are a measure of statistical significance; correct?

A. P values are a measure of statistical significance.

Q. Right. And, here, statistical significance was not achieved; correct?

A. We did not find a P value with regard to that result. We did find some other significant P values in this

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study, but the specific question of association between olmesartan and diarrhea among these patients, our P value was north of the traditionally accepted statistical significance cutoff, which is the one that we prespecified, .05.

Q. But you did not achieve statistical significance. That was the question I asked.

A. I believe I just answered --

Q. I thought you told me no.

A. I believe I just answered that we did not meet statistical significance with regard to the specific issue of olmesartan. I just thought it might be inaccurate to say that I did not achieve a statistical significance in that paper, because as you can see, there are some that do go by that threshold.

Q. But with regard to the question I asked, the answer is no; correct?

A. With regard to the

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association with olmesartan, the answer is, no, it was not statistically significant.

Q. Okay.

I had also wanted to ask you a question regarding your supplemental reliance list and that's been marked as Exhibit 7.

A. Okay.

Q. And you identify on the second page, under additional material, the FDA health safety announcement of July 3, 2013.

A. I do.

Q. That's something that was already in your report, though, wasn't it? I'd invite you to page 8 of your report. You can look at page 30 as well.

MR. SLATER: Are you accusing us of being too thorough?

MR. MURPHY: Not at all. I stick to the truth.

THE WITNESS: I would have to check to see if I reference it

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elsewhere, but my understanding of one's reliance list is that this was just a passing mention of what is common knowledge among those who are interested in olmesartan enteropathy, that there was an FDA notification. Perhaps we were being overly cautious with regard to the actual text of the health safety announcement.

BY MR. MURPHY:

Q. And just to round this out, on page 30 of your report --

A. I'm on page 30.

Q. Yes, sir -- at the second line, you reference the safety report again; correct?

A. Let me take a look and make sure that we're talking about the same thing.

Q. Sure.

(Pause.)

THE WITNESS: It does mention the same -- it does quote

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from that drug safety communications.

BY MR. MURPHY:

Q. Right. I just was trying to appreciate why it's listed as a supplemental reliance item when it's discussed twice in your report.

A. I admit it might have been inadvertent that we left it off the first time even though we -- even though I cited it. I'm not quite sure. But if you have any relevant questions related to that, I'd be glad to try to help.

Q. You also identify certain expert reports that were provided to you, general causation reports, in your supplemental list.

A. Yes.

Q. Did you consult with any of these experts while you were generating your report?

A. Well, if you're referring to these four individuals -- is that what you mean?

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Q. Correct.

A. -- well, three out of four, Tackett, Hutfless, and Kessler, I've never met personally, though I've certainly known about Dr. Kessler, who's in certain ways a public health hero, so I knew who he was, but I've never talked to him or met him in person.

Dr. Leffler is an investigator in celiac disease and so we've collaborated on a few projects --

Q. I just -- no disrespect, but my question was, did you correspond with them or collaborate with them in any way to generate your report?

A. I've never spoken to Dr. Leffler about the generation of my report or about the -- what went into this report, but I just wanted to make sure I understood properly, because I correspond with him about other matters relating to celiac disease, research and collaborations, fairly regularly.

Q. Dr. Lebwohl, let me ask you

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to turn to page 5 of your report, please.

A. I'm on page 5.

Q. Okay.

And toward the -- about the bottom third of the page, there is a sentence that begins, "There is not a single."

A. I see it.

Q. And the sentence reads, "There is not a single invariable presentation for this condition, and the condition is ultimately diagnosed based on the clinical presentation and course, with particular attention to positive dechallenge or rechallenge."

Did I read that right?

A. Yes, you did.

Q. Is it necessary to have rechallenge to establish that olmesartan is the cause of sprue-like enteropathy?

A. Can you repeat that question?

Q. Sure. Is it necessary to have rechallenge to establish

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definitively that olmesartan is the cause of sprue-like enteropathy?
A. No. Rechallenge certainly is something that we pay particular attention to and can be compelling, but it's not a -- it's not a necessary component.
Q. Is it necessary to have dechallenge to establish definitively that olmesartan has caused sprue-like enteropathy in a patient?
A. I think that if the question is to establish to a reasonable degree of medical certainty, I don't think that dechallenge is always necessary; but, unfortunately, someone could be taking olmesartan, become so ill that the patient actually dies before the olmesartan is withdrawn and sufficient evidence can make it, to a reasonable degree of medical certainty, that it was in fact the olmesartan that was causing the enteropathy.
Q. Short of a patient's demise,

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is it necessary to have dechallenge?
A. I suppose that there are patients who could be lost to follow-up and for whom we don't have definitive dechallenge data, but still be very suspicious that these patients have olmesartan enteropathy, in fact, suspicious to a reasonable degree of medical certainty.
Q. What is involved in dechallenge; that is, does it require total clinical and histologic resolution?
A. No. Dechallenge involves withdrawal of the offending agent and it involves a change in those various parameters for the better, though there's not a definitive parameter that is essential.
For example, if you have someone who has a dechallenge after years of so-called refractory celiac disease, has been gluten-free, not getting better at all, and then goes off Benicar and has significant improvement, even without

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histologic evidence of that, that to me is a convincing dechallenge.
Q. Are there instances where patients who have celiac disease see resolution in that celiac disease without gluten being removed?
A. Can you repeat the question?
Q. I'll restate the question.
In order for celiac disease to resolve, is it necessary to discontinue gluten?
A. Celiac disease is well defined as gluten-induced enteropathy and anyone who makes that diagnosis will recommend withdrawal from gluten.
But there are people who, for example, get diagnosed with celiac disease -- and this is not uncommon -- they get diagnosed with celiac disease as a child, for example, they are put on a gluten-free diet and then as they push young adulthood, based on the misperception that celiac disease is something you can, quote, unquote, grow

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out of, some people are put back on gluten and some of those patients do get very ill again.
Others have no apparent ill effect, but if you were to investigate them, they clearly have ongoing gluten-induced enteropathy. Some of these patients feel well, but if you check a bone density, they have severe osteoporosis.
So you can imagine a scenario where you have a patient who was diagnosed with celiac disease, really stayed on gluten for most of their life, feels fine, but they still have celiac disease.
Q. With regard to the condition sprue-like enteropathy, there are cases of sprue-like enteropathy that are reported to have nothing to do with olmesartan; correct?
A. You know, the term "sprue-like enteropathy" is almost exclusively reserved to the olmesartan

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literature, at least these days. Now, there are people who have villous atrophy in the absence of celiac disease who -- whose villous atrophy is unrelated to olmesartan, people who've actually never taken olmesartan.

The term for that has a few -- there are a few different terms. There's nonceliac enteropathy. There's seronegative villous atrophy. There's seronegative sprue and so on and so forth.

And so if that's what you are asking, sure, one can have villous atrophy without the presence of either celiac disease or olmesartan. There are a number of other causes.

Q. And -- let's just take seronegative villous atrophy for an example. Are you aware of instances where patients who've had seronegative villous atrophy have the situation resolve spontaneously?

A. I've certainly read of such

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cases. For example, after an acute infection, one can have transient villous atrophy that gets better really without intervention aside from perhaps supportive care. Those typically are rapid resolutions.

I'd be hard-pressed to come up with an example of someone who's had villous atrophy for a longer period of time, who spontaneously remits without any change. To be honest, that's probably because these patients make their way to healthcare providers and we try different things to correct this abnormality.

But, no, I think it would be pretty unlikely to encounter such a case where someone had villous atrophy and really no intervention was done and then they spontaneously remit.

Q. Now, let's get back to what we've been referring to as olmesartan-associated enteropathy. Okay? Am I correct that in your view, it is

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necessary to have dechallenge --

A. Well -- are you finished with your question?

Q. No, you started talking, so I stopped.

A. Apologies.

MR. SLATER: Slow down.

BY MR. MURPHY:

Q. To definitively establish whether olmesartan is responsible for sprue-like enteropathy, is it necessary to have dechallenge?

MR. SLATER: Objection.

You can answer.

THE WITNESS: I think that I've answered that question. There are a number of cases or scenarios where one cannot have a dechallenge, but still, to a reasonable degree of medical certainty, make the diagnosis of olmesartan enteropathy.

BY MR. MURPHY:

Q. In what circumstances is it

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possible to do that?

A. Could I ask that my answer be read back from earlier this afternoon when you asked earlier short of death of the patient? Can I have that answer read? Because I believe I've been asked this before.

MR. MURPHY: If you can find what he's asking for, Kim, please do.

- - -

(Whereupon, the court reporter read back from the record as follows:

"QUESTION: Short of a patient's demise, is it necessary to have dechallenge?

"ANSWER: I suppose that there are patients who could be lost to follow-up and for whom we don't have definitive dechallenge data, but still be very suspicious that these patients have olmesartan enteropathy, in fact,

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suspicious to a reasonable degree of medical certainty."

- - -

THE WITNESS: I believe that's the same question, and so I hold by the answer.

BY MR. MURPHY:

Q. So in that instance, there would not be definitive evidence of dechallenge, but mere suspicion; correct?

A. I think that we're moving around the word "definitive." I think that, initially, you asked me about whether we were definitive about olmesartan enteropathy and I used the word definitive when talking about a definitive dechallenge, that means are we sure that this patient stopped the olmesartan.

I think that it's still possible to have a reasonable degree of medical certainty that a patient had olmesartan enteropathy even short of well-documented dechallenge data.

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Q. Now, with regard to the definitive dechallenge, to use your term --

A. I -- if I may interrupt, I'm not sure if we mean the same thing by that, but if I can define -- or why don't you --

Q. And that's what I'm asking you to do, is to define what an effective dechallenge entails.

A. If a patient is no longer taking olmesartan and there is improvement of any of -- of those parameters that make up the clinical phenotype of olmesartan enteropathy.

Q. And is there a time course for this dechallenge period where the patient gets better, so to speak?

A. It's hard to be too dogmatic about a cutoff. Of course, people take olmesartan in discrete doses. It's typically taken as a once-daily -- once-daily medication; and between those doses, one does -- even if one is not

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taking olmesartan, because of the half-life of olmesartan, one can reasonably say they're still on olmesartan.

That said, if someone stops it for more than a day, clinical improvement or resolution can be quite rapid, within a day or two. I've seen that personally. In contrast, clinical resolution for some people might take significantly longer.

Q. Why is that so?

A. I think that it's probably analogous to gluten withdrawal in celiac disease, that the cause of the symptoms, even if it was clearly gluten in the case of celiac disease or was clearly olmesartan in the case of olmesartan enteropathy, can still result in lingering effects even beyond the half-life or the presence of the offensive agent in the system.

One could speculate why people have variable rates of

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improvement, but it's certainly something we've observed in both of those conditions.

Q. You also state in your report, Doctor, that the condition most often misdiagnosed -- or I should say that olmesartan is most often misdiagnosed as celiac disease, that's a position you take --

A. Could you cite in my report, direct me to it?

Q. Sure. Bear with me.

If you look at page 5 --

A. I'm on page 5.

Q. Okay. At the bottom, last line, "This condition has been misdiagnosed, most often as celiac disease in many patients, or other inflammatory disorders due to the similar clinical presentations" -- and I'm sorry, for completeness -- "and a lack of knowledge about olmesartan enteropathy in the medical community."

A. At this point, much of the

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literature --
Q. I didn't ask -- that was just a predicate to my question.
A. Go on.
Q. Okay. Your point here is that sprue-like enteropathy is often misdiagnosed as celiac disease; correct?
A. It is often misdiagnosed early on as celiac disease.
Q. And we touched on this earlier, but I want to make sure that we're clear: With regard to the subject of the 2012 Rubio-Tapia paper, certain of those individuals were misdiagnosed as having celiac disease; correct?
A. It appears that the primary reason they were being cared for by this group, in fact, was that there was a frequent misdiagnosis of celiac disease and that the initial impression had been celiac disease.

- - -

(Deposition Exhibit No. Lebwohl-8, 2014 Paper "Sprue-like

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Enteropathy Associated with Olmesartan" by Cartee and Murray, was marked for identification.)

- - -

BY MR. MURPHY:
Q. Doctor, you've been handed what's been marked as Exhibit 8 to your deposition. It is a copy of the Cartee-Murray paper -- Cartee, C-A-R-T-E-E, and Murray paper -- which you mentioned earlier.
(Pause.)
BY MR. MURPHY:
Q. You have it in front of you, Doctor?
A. I do.
Q. And this paper was a follow-up to the Rubio-Tapia paper; correct?
A. Well, it certainly was published after the Rubio-Tapia paper and, in that sense, I would agree it's a follow-up, though it's not clear to me that it's those patients that were

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followed up.
Q. In this paper we've marked, that is Cartee and Murray, one of the things that the authors note is that certain of the patients seen at the Mayo Clinic had underlying celiac disease.
A. Can you show me specifically what you're referring to?
Q. If you would turn to page 420, that's also the pagination is 4 out of 8 --
A. Okay.
Q. Are you with me?
A. Yeah.
Q. -- the right side, third full paragraph, "After the diagnosis and treatment for OAE," which is olmesartan-associated enteropathy, "several patients seen at the Mayo Clinic likely had underlying celiac disease as evidenced by symptoms with reinstitution of gluten into the diet and strong family history of celiac disease."
A. I see it.

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Q. You see that?
A. Yes.
Q. So that's what I'm referring to.
A. Yes.
Q. No dispute about that.
A. I have no dispute that that's what's written here.
Q. Do you think that's inaccurate?
A. No reason to --
MR. SLATER: Objection to the form.
You can answer.
THE WITNESS: I have no reason to think that that's inaccurate.
BY MR. MURPHY:
Q. Do you know how many of those patients were, in fact, misdiagnosed?
A. Well, the --
MR. SLATER: Objection to the form.

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You can answer.
THE WITNESS: They say the word "several." That's traditionally understood as somewhere between, I don't know, three and seven perhaps, though I think "several" is a vague term and I don't see any further specification beyond that.
I take them for what is written, several.
BY MR. MURPHY:
Q. Now, if you, on that same page, go to the left side of the page under the heading "Treatment," the second full paragraph --
A. I'm with you.
Q. Okay -- reads, "Once the possible role of olmesartan was recognized, the drug was stopped. Most, but not all, patients improved with drug withdrawal."
Do you see that?
A. I do.

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Q. "Some more ill patients required budesonide (a topical potent corticosteroid) to initiate a clinical response, control diarrhea, and accelerate healing."
A. I see that and I see that they reference not only their own experience, but that of another article relating to olmesartan.
Q. But, again, the Rubio-Tapia group all were said to improve with withdrawal of the medicine; correct?
A. In that separate paper which, my interpretation, is a separate group of patients for whom the inclusion criterion was to improve upon discontinuation of olmesartan, those patients that were predefined to improve off olmesartan as a condition for being in that initial case series was, in my interpretation, a limited subset of patients who have come through the Mayo Clinic with olmesartan enteropathy.
Q. And so your interpretation

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is that there are two separate groups of patients discussed in Rubio-Tapia and Cartee-Murray.
A. My interpretation of the Cartee-Murray paper is that this is an aggregate experience of the Mayo Clinic, so that will include those that they have written up previously, such as in the Rubio-Tapia paper, but based on what they're describing here, indicates that there are other patients that either didn't fit the inclusion criteria for the first paper or they only came to the Mayo Clinic for evaluation and were diagnosed after that first paper was written up.
Q. Okay.
Now I'd like to take you back to your report and page 6 of your report. A little more than midway down in that first full paragraph, you write, "Upon hearing about this from Dr. Green, my colleagues and I reviewed the charts of our most treatment-resistant patients, and were struck by the fact that

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olmesartan was a common feature."
That's what you wrote.
Right?
A. I see it. I remember writing it and I remember living through it.
Q. Okay.
This chart review that you reference in your report, that is at least part of what you rely upon in reaching your ultimate conclusion and opinion in your report; correct?
A. I certainly was struck by that and what I would argue is that if I had only heard about Dr. Murray's or the Rubio-Tapia initial case series from the Mayo Clinic Proceedings and I had not come up with any patients on my own or heard of any others outside Mayo, then I would have some questions about why we're not seeing it elsewhere.
When I saw, with my own eyes, my patients getting better, it did inform my opinion, which was then

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subsequently reinforced significantly by the case reports and series that cropped up from around the world in the ensuing years.

Q. So my question was, your chart review was something that you rely upon at least in part in reaching your conclusion and the opinions set forth in your report; correct?

A. So I included this in my report because there was nothing else published on it aside from that coming out of the Mayo Clinic, and so this got me interested in this condition. It spurred me to study this condition and publish on this condition and to keenly follow the literature on it, and that's really what confirmed my opinion.

Q. And one of the things that you write here is that all of your patients or many of them got better when they discontinued olmesartan; is that right?

A. I wrote that this resulted

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in some of the most dramatic clinical improvements I've witnessed as a physician.

Q. And how many of your patients got better when you -- when they discontinued olmesartan after you had this conversation with Dr. Green?

A. I can't remember the exact number, but all of the patients that I reached out with -- that I reached out to got better, either entirely or nearly entirely.

Keep in mind, this was not a formal process. We were not keeping a registry of olmesartan enteropathy patients --

Q. Had all -- I'm sorry. Had all of them received olmesartan therapy?

A. The patients that I reached out to --

Q. Yeah.

A. -- were the ones who Dr. Green and I and my colleagues, after he talked to Joe Murray -- we basically just

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off the top of our heads, we're thinking, who are these patients that are keeping us up at night? We don't have a formal list of this, but all doctors have patients when they're tossing and turning are worried that things just aren't going the right way. And we then started to look in their charts and it was amazing, Benicar, Benicar, Benicar.

And so those who were on Benicar, which was a substantial proportion of those patients who keep us up, were contacted and the rest is described here.

Q. But in terms of number, you don't know how many there were.

A. I hesitate to, off the top of my head, tell you how many.

Q. That's fair.

Can you tell me how many of those patients, the ones that kept you up at night who clearly were on Benicar, had a family history of celiac disease?

A. I certainly don't remember.

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It's something that I often ask about with regard to my impression that someone themselves have celiac disease. Some of those patients, in fact, had a diagnosis of refractory celiac disease, but none of them ended up with the diagnosis of celiac disease by the time we sorted this out.

They're all eating gluten and doing well.

Q. But back to the call of my question, are you able to tell me how many of those folks had a family history of celiac disease?

A. No, I'm not. Family history of celiac disease --

Q. Do you --

A. I'm not finished -- is a fraught subject, though, because we have to recognize celiac disease remains underdiagnosed in this country.

And so knowing if someone has a family history of celiac disease or not can be difficult to ascertain because

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a lot of people haven't been tested for celiac disease.

Q. Finished?

A. Yeah.

Q. Okay. How many of those folks had symptoms onset, that is, GI symptoms, within the first year of their olmesartan therapy, of the folks that you contacted?

A. I'm hesitant to give a concrete answer because I can't really provide a list off the top of my head. I would say that in general, when we got down to it and we figured out that they were on olmesartan -- and that was basically just by looking at an old record -- at the time, we didn't even know how long they'd been on it simply because when a patient comes in for an assessment, if you don't know that olmesartan is the culprit and you don't know about this entity and they give you a list of ten medications, which is not uncommon, we don't ask for each one how

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long have you been on it.

For those whom we then figured out they had olmesartan enteropathy, we would ask. I would say as a rule, not a hundred percent and every rule has an exception, in general, they were on it for quite some time and that would be probably more than a year in the majority of patients.

Q. How many of those folks, that is, those to whom you reached out and advised to discontinue olmesartan, were taking another blood pressure medicine, that is, an antihypertensive, along with olmesartan?

A. I'm not sure how many precisely. Being on more than one blood pressure medication is not uncommon and as is widely known, olmesartan frequently comes as a combination pill. I believe the trade name is Azor and it's olmesartan hydrochlorothiazide or Azor HCT. And so I'm not sure if that would technically count as two medications or

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one. It has two active ingredients in one pill.

But I don't know the answer right now.

Q. You don't know. Okay.

Were any of those patients that you reached out to and advised to discontinue olmesartan on immunosuppressants?

A. Many had been tried on immunosuppressants either by me or prior to there having been referred to me, commonly budesonide.

Budesonide is a steroid that has minimal systemic effects or more modest systemic effects compared to prednisone that we often resort to using when we're really not sure what's going on in terms of the cause of one's persistent symptoms and/or histologic abnormalities because some patients have a response.

Often, unfortunately, the response is either short-lived, i.e.,

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transient, or recurs upon cessation of immunosuppression, and that was often the case in our patients.

Q. But getting back to the call of my question, which was how many of those folks were on immunosuppressants, you are not able to tell me how many; correct?

A. Some were on at the time --

Q. My question was, are you able to tell me how many? And I mean no disrespect, but I just want to get the answer and move on. I don't --

A. I'm not even sure if it was the majority of patients or the minority. Often the immunosuppressant is sort of peppered in their history. They're on it for some time. They're off it for some time because of transient improvement.

Q. So some may have been on, some may not have been on.

A. That's right.

Q. But you don't recall.

A. Precisely, no, how many, no.

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Q. The same question with regard to steroids: Do you know how many of them had been receiving steroids?
A. When you asked about immunosuppression, I considered steroids --
Q. You considered the same --
A. Well, they're not identical.
Q. No, I meant same in terms of the question.
A. I would say the answer is the same, but of course there are immunosuppressants that are not steroids and some may have been on those.
Q. So --
MR. SLATER: You need a break?
THE WITNESS: Maybe another two minutes.
MR. SLATER: Okay. It looked like he was pushing back.
BY MR. MURPHY:
Q. So with regard to these treatment-resistant patients of yours

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that were keeping you up at night, none of them were getting better before you suggested discontinuation of olmesartan; is that correct?
A. What I'd say is, none were having a sustained improvement. Some patients had periods where they were getting better, in fact, in some cases, due to the fact that they'd been off olmesartan for a period of time and then were ill again when they were back on the olmesartan.
In some patients, they had gotten a little better because they were on budesonide for a period of time, but then ill again, either after tapering the budesonide or being back on the budesonide.
They were not all in dire straits at the time of our conversation, but they had all been there and were not having a sustained improvement until they stopped the olmesartan for good.
Q. When did you review these

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charts?
A. I can't give you the exact date, but I believe it was in April 2012. And I would add that it wasn't a formal process where we actually looked at either physical or electronic charts. It was more, frankly, like shooting the breeze with colleagues and we were just going over patients in person and then later, one by one, discovering that they'd been on Benicar.
Q. Did you conclude that any of these patients had been accurately diagnosed with celiac disease?
A. I concluded that none of them ended up really having celiac disease. At the time that I contacted them, I didn't know. And some of these patients, when I told them about this report that we had -- and it wasn't in the formal write-up, but this is what we heard from our colleagues that it might be the Benicar -- you know, they started by being open to the possibility.

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Frankly, they were desperate in looking for anything, but their responses were so dramatic that it was quite convincing.
And then, when they saw me back again and they were better, I then broached the possibility of restarting gluten in their diet. Some were hesitant to begin with because they had sort of been trained to think that gluten was the source of all of their problems. They turned their kitchens upside-down and indeed their lives upside-down.
But with some encouragement of the possibility that maybe they don't need to be on this very difficult diet, they all ended up trying eating gluten again and they all remained well.
Q. You told me that you believe that it was in April of 2012 when you reviewed the charts; correct?
A. Best as I can remember, I would put it at April of 2012.
Q. When did you reach out to the patients?

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A. So it was within a day or two of discussing that with Peter Green and colleagues. It was quite quick. I really was struck by how much Benicar there was among these sick patients and so I felt that if I could do something as a physician to help these patients, I should reach out to them as soon as I could.

MR. MURPHY: Counsel, I'd request a production of the redacted -- properly redacted -- patient charts.

MR. SLATER: Our position's in the response to the dep notice.

MR. MURPHY: That's fine. My request is on the record. I note your position.

We can take a break at this point if you want.

MR. SLATER: And I'll just state it for the record, and you can ask Dr. Lebwohl, he doesn't even own those charts. They

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belong to the institution. There's not a chance in the world that we're going to be able to produce those.

What you would have to do to get those would be massive hoops and it would have to be a litigated issue.

MR. MURPHY: Understood. We can break now if you wish.

MR. SLATER: Sure.

(A recess was taken from 2:20 p.m. to 2:33 p.m.)

MR. MURPHY: Back on the record.

BY MR. MURPHY:

Q. Doctor, let me ask you to turn to page 7 of your report.

A. I'm on page 7.

Q. And just I guess beyond the midway point of that -- that full paragraph, there is a sentence that begins, "Given the information."

A. I see it.

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Q. "Given the information we have received from Dr. Murray and our own experience of dechallenged patients who then improved, we reviewed the records that we had collected and found that, of 72 patients with seronegative villous atrophy, 16 (22%) were ultimately attributed to olmesartan use."

Do you see that?

A. I see it.

Q. And then further down, there is a cite to the DeGaetani paper; correct?

A. Correct.

Q. And so that review and what you observed was reflected -- is reflected in the DeGaetani paper.

A. That's right.

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(Deposition Exhibit No. Lebwohl-9, 2013 Paper "Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma" by DeGaetani,

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et al, was marked for identification.)

- - -

BY MR. MURPHY:

Q. Now, when you write in your report, "were ultimately attributed to olmesartan use," does that mean that it was caused by olmesartan?

A. What I mean is, even if at the time we were preparing this analysis we did not attribute it to olmesartan, in the middle of that preparation, we discovered that those ultimately were caused by olmesartan.

Q. Okay. So the 16 of the 72, you ultimately concluded that those folks with seronegative villous atrophy, they had -- their condition was caused by olmesartan.

A. Yes, we concluded that olmesartan was the culprit medication, as we characterize in that paper.

Q. Was this group of 16 told to discontinue olmesartan?

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A. These were largely not my own patients and my interpretation is that in all of them, or nearly all of them, they clinically improved after stopping the medication.

Q. And when did you and your colleagues learn that they had got better after discontinuation of olmesartan therapy?

A. I can't tell you in terms of what the date was that that was ultimately determined, but it was between the time of when Dr. Murray's group first reported this problem or possibly even before, when Dr. Murray first told Peter Green about this condition --

Q. So sometime after 2011?

A. As far as I can tell, these patients were all characterized after we learned about it, which was after 2011.

I have to introduce a caveat, though. While I was involved in the design of this study, I did not personally care for each of these

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patients, nor did I review all the charts of those who were attributed to have olmesartan enteropathy, and so I can't give you a definitive answer about the chronology of their dechallenge data.

I will say that this was a study that when it was first conceived was not meant to be about olmesartan and, in fact, we had many more patients who we initially had classified as something else; but once we discovered the olmesartan link, we then concluded that their disease was olmesartan related.

Q. So in terms of the workup of these patients that occurred in 2011 or earlier, you were not involved in the workup of all of these patients; is that your testimony?

A. I was not personally involved in the workup of all of these patients. This was a group that was characterized based on a number of ascertainments.

To the best of my

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recollection, the way that Dr. DeGaetani under the mentorship of Dr. Green came up with this list was a mix. It was a search of known celiac disease patients for whom a negative celiac disease serology was present and it was also an informal process of asking colleagues, who do you know -- which one of your patients has villous atrophy and negative celiac disease serology, can you come up with any, and it was sort of collected in that fashion.

Q. Were any of these patients your patients?

A. I believe so, though I can't tell you that I can remember which one of these or ones of them they were. Certainly the majority were not my patients, but I believe that I had one or more patients in this group.

Q. Any of the 16 that are referenced in your report as you referenced this article -- any of the 16 your patients?

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A. I believe I just answered. So of those 16 that were attributed to olmesartan, I believe I may have had one or more, but I'm not sure.

Q. So you would have worked up those patients at some point in an effort to determine what the cause of their villous atrophy was; correct?

A. Right. Those who were in my care, one or perhaps more, would have been under my care.

Q. Let me direct your attention, Doctor, to the DeGaetani report and specifically table 3. I think you're there.

A. I'm there.

Q. And at table 3, we see data on the 16 patients; correct?

A. I see it.

Q. And it shows that all of the 16 showed clinical improvement when they were placed on steroids and immunosuppressants; correct?

A. I see clinical

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improvement/IS, which stands for immunosuppressants. I'm not sure if that refers to steroids in every one of those cases, but it does indicate that all of them had a degree of clinical improvement on immunosuppressants, which likely often included steroids of some sort.

Q. And only two of them had -- only 2 of the 16 had biopsy showing evidence of improvement after olmesartan was discontinued; correct?

A. Let's take a look.

Q. Sure.

A. That's two columns over. The column in between -- or it's, rather, three columns over -- it looks like in between those two columns, though, the patients all relapsed when off immunosuppressants and then clinically improved after stopping olmesartan, it looks like, in 16 out of 17. The one is indicated with a question mark. Perhaps that was related to loss of follow-up but --

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Q. Doctor --

MR. SLATER: Wait. Don't interrupt him. He was trying to clarify his answer to the last question.

MR. MURPHY: Is that what you were doing, clarifying your answer to the last question?

THE WITNESS: You asked me to comment on --

MR. MURPHY: No.

THE WITNESS: -- biopsy --

MR. MURPHY: I asked you --

MR. SLATER: Time-out, time-out. Ken, you cannot interrupt him while he's talking. Let him finish his answer. Even if you think it's nonresponsive, you know what you're supposed to do. So let's just do that. Okay?

MR. MURPHY: Let's go off the record, Kim.

- - -

(A discussion off the record occurred.)

- - -

MR. SLATER: I don't want to go off the record. Whatever you're trying to do is fine, but when he's talking, it's not appropriate to cut off his answer. That's all I'm saying. That's it. That's all I'm saying.

MR. MURPHY: Fair enough.

MR. SLATER: I don't know what he's going to say. For all I know, it's going to be, "and let Slater jump out the window." I have no idea, but I just don't want to cut him off in the middle of his answer.

MR. MURPHY: That's fine. So, doctor, I'm going to take a step back and I'll ask the question of you and we'll pick up there.

And my question to you is, isn't it the case that only 2 of

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the 16 had a biopsy evidence of improvement after discontinuing olmesartan?

THE WITNESS: That's not the case. This was published in -- let's check the year -- 2013. It's very possible -- I would even say likely -- that others had subsequent biopsies, but those biopsies either were not performed or were not available at the time of publication of this paper.

BY MR. MURPHY:

Q. Okay. Are you finished?

A. Yes.

Q. All right.

With regard to this chart and the data that is set forth in this chart, as to the 16 patients in question, there are only 2 that had a biopsy with evidence of improvement after discontinuing olmesartan; correct?

A. If by chart you mean the table --

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Q. Table --
A. -- in this manuscript that was published in 2013 --
Q. Table 3.
A. -- biopsy data is only noted in 2, but I believe that others likely had biopsies showing improvement after stopping the medication after the publication of this table.
Q. And at the outset, all of these patients were referred with a diagnosis of refractory celiac disease; correct?
A. When you say all of these patients, do you mean all of the patients in this study or all of the 16?
Q. 16.
A. I'm not sure and the reason I say that is that while refractory celiac disease or poorly responsive celiac disease is indeed a common misdiagnosis given to people who are ultimately proven to have olmesartan-induced enteropathy, there are

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other diagnoses that patients are branded with that are subsequently withdrawn.
So I'd have to check a little bit more closely in terms of the description of those 16 patients, if they are so described in the paper.
Q. And refractory celiac disease and unclassified sprue are two distinct conditions; correct?
A. Refractory celiac disease indicates the clinician's belief that this patient has celiac disease that's no longer responsive to the gluten-free diet. Unclassified sprue is more generic and indicates some less certainty.
So, for example, if you have a patient who is negative for the necessary HLA-DQ2 and DQ8 haplotype, the genes that are necessary for celiac disease, they can phenotypically look just like someone with refractory celiac disease, but we generally label them as having unclassified sprue because we do not believe that they have celiac

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disease.
Then there are others who are positive for that genetic complement who we're just less confident that they have celiac disease to begin with, whether because they never responded at all to a gluten-free diet as compared to someone who initially responded and then loses the response.
And so there is a bit of interchangeability and overlap, but I would say that in terms of those Venn diagrams, there's also plenty of separation, too.
Q. In here, that is, in the paper, it's stated that certain of these patients were initially labeled with unclassified sprue. Do you recall that?
A. I believe that it's noted what the ultimate diagnosis was. As for initial diagnosis, I would have to go back and double-check.
Q. Let me -- maybe this will help you -- direct your attention to page

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650.
A. Sure.
Q. Under the discussion section?
A. Okay.
Q. Toward the end of that first paragraph under discussion.
A. It's the middle column of page 650?
Q. Yes, sir.
A. Towards the bottom of that column?
Q. No. First -- toward the bottom of that first paragraph.
A. Oh, okay.
I see it.
Q. So there were a number who were initially labeled with unclassified sprue; correct?
A. That's right.
Q. Do we know how many?
A. I don't believe that's specified, though perhaps it's in the tables.

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Q. And were these folks later determined to have olmesartan-associated enteropathy?
A. That's what it says, is that the number of patients who were initially labeled with unclassified sprue were -- who were ultimately found to have villous atrophy as a result of olmesartan use, yes.
Q. But they didn't have that, the diagnosis of, before 2013; correct?
A. It's very possible that they had a diagnosis of unclassified sprue years before, but only after April of 2012 with the revelations by Dr. Murray did they then get evaluated for olmesartan enteropathy.
Q. In your report, you mentioned that Dr. Green told you of Dr. Murray's findings. You state that early in your report. We can go there if you need the specific reference.
A. Are you referring to page 6?
Q. Yes.

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A. Okay.
Q. In your conversation with Dr. Green, did he tell you how many patients failed to improve when olmesartan was discontinued?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I'm not sure I understand the question fully. Whose patients are we talking about here?
MR. MURPHY: The patients that Dr. Murray had seen.
MR. SLATER: Objection; lack of foundation.
MR. MURPHY: Sure. I'll take one step back to the extent there's some confusion.
BY MR. MURPHY:
Q. Dr. Green told you of Dr. Murray's work and his findings; correct?
A. He did. He mentioned that conversation he had.
Q. Did Dr. Green tell you that

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certain of Dr. Murray's patients failed to improve when olmesartan was discontinued?
MR. SLATER: Objection; lack of foundation.
You can answer.
THE WITNESS: At that time, I don't believe he mentioned lack of improvement. It was a rather short explanation and paraphrasing and simply pointed out that it appeared that Benicar was causing these symptoms.
BY MR. MURPHY:
Q. Let me ask you to turn to page 17 of your report.
A. (Witness complies.)
Q. Bear with me one second.
(Pause.)
BY MR. MURPHY:
Q. In the first full paragraph on page 17, you write in part, "The case that the relationship between olmesartan and enteropathy is causal is well

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established based on the numerous dechallenge studies described in the case series and reports above."
A. I see that.
Q. In certain of those or at least in one of those reports above, we saw that there were patients who did not -- whose symptoms didn't resolve when olmesartan was discontinued; correct?
MR. SLATER: Objection; lack of foundation.
THE WITNESS: Can I ask which studies you're referring to?
BY MR. MURPHY:
Q. Is it your position, Doctor, that none of those studies show that there were some whose symptoms did not resolve when olmesartan was discontinued?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I am asking for clarification on which studies we're dealing with. I cited a number of studies above and I'd be

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interested to know what are the studies in question right now.
BY MR. MURPHY:
Q. Okay. DeGaetani.
A. And can you repeat the question regarding DeGaetani?
Q. So my question was, isn't it the case that there were some patients who did not see their symptoms resolve when olmesartan was discontinued?
A. My interpretation of the DeGaetani data as shown in table 3 is that of 16 patients, 15 evinced clinical improvement after stopping the medication and the last one is denoted by a question mark, and perhaps we can see if that's further -- further characterized, but likely indicates that their status was unknown at the time of this being written up, either that patient was lost to follow-up or the follow-up time was deemed to be too short to be sure about a lasting improvement.
MR. SLATER: Do you want him

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to show you in the study where that's discussed? Because he's looking for it. He's going to give it to you so --
MR. MURPHY: I'm not asking for that.
BY MR. MURPHY:
Q. Earlier on when we discussed --
MR. SLATER: He's looking for the --
THE WITNESS: I'm trying to clarify that question mark symbol.
MR. MURPHY: Oh, I'm sorry. Sure. Sure.
THE WITNESS: If you'd like to direct me to where that's indicated or further expounded upon in the manuscript, that might save us some time, but I'll take a look myself.
MR. SLATER: I can save the time.
MR. MURPHY: He can take as

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long as he wants.
MR. SLATER: Okay.
(Pause.)
THE WITNESS: As far as I can tell, at least on my review, I don't see a further explication of the question mark denoted in the table indicating that 1 out of the 16 olmesartan enteropathy cases had a question mark with regard to clinical improvement.
I would say that it appears that that patient had the shortest follow-up time of all of the patients with olmesartan enteropathy, at least at that time.
BY MR. MURPHY:
Q. When we were discussing the Cartee and Murray paper, I understood you to say that the patients discussed in that paper were not the same group of patients as were discussed in the Rubio-Tapia paper; is that right?

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A. I believe there might have been some overlap, but they were not identical lists of patients, that's right.
Q. And we also saw that in the Cartee and Murray paper, the authors stated that most, but not all, of the patients improved with drug withdrawal; correct?
MR. SLATER: Objection. You can answer.
THE WITNESS: It does say that most, but not all, patients improved with drug withdrawal.
BY MR. MURPHY:
Q. Doctor, are you aware of any studies that show that increasing doses of olmesartan leads to a higher risk of sprue-like enteropathy?
A. If you're referring to dose in terms of milligram strength, I've not seen such data. Cumulative dose, as better defined as duration, does seem to indicate that.

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It's my belief, though, that if one had to compare 40 milligrams to 20 milligrams, for instance, we haven't seen that traditional sort of dose-response, but I would point out that this might be the case -- and I believe this is the case -- that that is because the minimal threshold for causing olmesartan enteropathy has been far exceeded in both of those cases.

And so we don't know what that minimal threshold is, but it's probably far below the traditionally lower dose given to adults at least who are prescribed olmesartan, which was -- is typically 20 milligrams.

Q. So it's your opinion that the dose necessary to trigger or cause enteropathy is less than the 20 milligram dose?

A. I suspect that people with olmesartan enteropathy have that enteropathy triggered or would have that enteropathy triggered by less than 20

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milligrams simply because it appears that we don't see that higher milligram dosages of enteropathy within the traditionally prescribed dosing parameters for adults shows that kind of response.

And so I would not at all be surprised if an individual with known olmesartan enteropathy, if that individual were exposed to a lower amount of olmesartan, if that -- I would be surprised if that did not also cause enteropathy.

And certainly in clinical practice, if a patient with known olmesartan enteropathy approached me and asked if it were safe to take, for example, a half dose of olmesartan, I would say stay away from that medication entirely.

Q. With regard to dose-response -- and I'm not talking about the long-term temporal aspect of dosage, but dose-response -- my question to you was

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whether there are any studies showing an increase -- that increased dosage of olmesartan leads to a higher risk of sprue-like enteropathy.

A. It appears that the threshold for inducing sprue-like enteropathy is well below the traditionally prescribed lowest dose of olmesartan enteropathy; and so to my knowledge, the typical doses that are studied are within that traditional dosing and we've not seen a dose-response within that traditional dosing.

Q. Now, what you've referred to essentially is the dose-response gradient in the Bradford Hill analysis; correct?

A. Dose-response is a component of Bradford Hill criteria, if that's what you're referring to.

Q. Indeed. If I can direct your attention to page 28 of your report, that is where you -- in that first full paragraph, where you initially address the Bradford Hill criteria for causality;

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correct?

A. I see that, yes.

Q. And would you agree that there are nine factors or points of consideration in the Bradford Hill analysis?

A. Do you speak in general or what I used here? And I ask because Bradford Hill criteria have been used variously throughout the literature and the exact number and terms for each criterion has varied.

Q. Now, with regard to the criterion that you identify in your report, is that exhaustive of the list of criterion with which you are familiar as being associated with the Bradford Hill analysis?

A. If I really wanted to be particularly florid in terms of explicating Bradford Hill criteria with every criterion that's been proposed to be included within Bradford Hill, I would have included more. This strikes me as

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sufficient.
I'm looking here and I do not see, for example, analogy, which is, of course, one of the Bradford Hill criteria that's used in some lists; but as I say, the Bradford Hill criteria has been enumerated variously in the literature.
Q. You identify analogy as one of the other criteria that you did not address. Is coherence another criterion you did not address?
MR. SLATER: Objection to the form.
You can answer.
THE WITNESS: Coherence is a heading of Bradford Hill criteria that has been proposed and used. In my enumeration of the Bradford Hill criteria, I do not specifically enumerate coherence.
BY MR. MURPHY:
Q. How about experiment?
A. Experiment is one of the

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Bradford Hill criteria that is sometimes used, though often this is merged with biological plausibility, and so I did not use a heading of experiment.
Q. Now, with regard to strength of association, as you address it in your report, you cite the Basson study as supportive or as satisfying that Bradford Hill criterion; correct?
A. I was particularly struck by Basson as an example of strength of association.
Q. So the answer to my question is yes?
A. I do cite Basson. That's not to say that that is the only evidence of strength of association.
Q. Okay.
And just so that we are tracking, was Basson a retrospective cohort study?
A. I would characterize it as a population-based cohort study, which by definition is also retrospective.

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Q. Now, with regard to strength of association, you did review the FDA Mini-Sentinel data, did you not?
A. I reviewed the FDA Mini-Sentinel data as well as its summary statement.
Q. And did that data show a statistically significantly -- a statistically significant association between olmesartan and sprue-like enteropathy?
A. Sprue-like enteropathy was not a diagnosis that was regularly being -- regularly being captured in the FDA's data at the time, so they had to rely on some surrogates.
Q. And the -- one of the surrogates upon which the FDA relied was celiac disease; correct?
A. They did. They did. And that is plausible. It makes sense to do that because as we are now aware, many patients with sprue-like enteropathy due to olmesartan are initially misdiagnosed

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as having celiac disease.
Q. And with regard to that surrogate celiac disease, there was not a statistically significant correlation shown, was there?
A. There was an association that was concerning enough to make it into a drug safety communication that notes that at a two-year minimum exposure which correlates with the long latency observed in literature and case reports, and so coherent with what we've been seeing in the literature, olmesartan users had a higher rate of celiac disease diagnoses in claims and administrative data than users of other ARBs.
Whether statistically significant or not, it was enough to be alarming to the FDA.
Q. Was it statistically significant?
A. I don't see that commented upon. I would add, though, that statistical significance is -- especially

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in emerging entities, is not something that is be all and end all, nor is a nonsignificant result a prompt to no longer be concerned.

There have been clinical trials, for example, in which rare adverse events have occurred in treatment arm where if one were to apply a statistically significant test to that event happening in treatment arm versus placebo, the P value would land north of .05 and, yet, those events in some cases, because they are either so severe or deemed sufficiently likely to be related to the intervention, might cause a trial to be halted, even without statistical significance, provided that those adverse events are adequately reported and disseminated by the sponsor of the trial.

MR. MURPHY: Move to strike as nonresponsive.

BY MR. MURPHY:

Q. Doctor, with regard to the ROADMAP data -- you're familiar with the

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ROADMAP data, are you not?

A. ROADMAP is an acronym for a clinical trial of olmesartan, if that's what you're referring to.

Q. I am. That data was null for intestinal-related adverse events; correct?

MR. SLATER: Objection.

You can answer.

THE WITNESS: ROADMAP to my knowledge was not designed to measure intestinal adverse events.

BY MR. MURPHY:

Q. Are you not able to answer the question? My question simply was whether it was null for intestinal-related adverse events.

MR. SLATER: Objection.

You can answer.

THE WITNESS: You might be referring to a secondary analysis that was published in the Mayo Clinic Proceedings as a letter to the editor in response or after

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the publication of the article by Rubio-Tapia and colleagues, "Severe Sprue-Like Enteropathy Associated with Olmesartan."

If that's the case, and if that's what you're referring to -- is that what you were referring to when you used the term "null"?

BY MR. MURPHY:

Q. Your understanding is that that piece that you're referring to deals with the ROADMAP data; correct?

A. That letter is a secondary analysis of ROADMAP data assessing whether a certain kind of outcome, which was not predetermined nor measured in such a way that it would correlate closely with sprue-like enteropathy, that is the letter we're referring to.

Q. We're talking about the same thing.

A. We're talking about that publication.

Q. Right, we're talking about

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the same document.

A. We're referring to the same document by Menne and Haller, "Olmesartan and Intestinal Adverse Effects in the ROADMAP Study." We're referring to the same document. Are you asking questions about that document?

Q. You answered the question. My question was in terms of the data and what you've classified is, the data was discussed in the Menne paper and we are agreed that that data was null for intestinal-related adverse events; correct?

MR. SLATER: Objection; lack of foundation, mischaracterization.

THE WITNESS: I believe it's deceptive to hold up a randomized trial publication that subsequently evaluates a secondary long-term finding that the initial trial was never designed, nor adequately powered, to detect, for

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which there were no active surveillance mechanisms to pick up this outcome, and then to use the imprimatur of a randomized trial and the acronym from that randomized trial to somehow prop up the quality of such a study.

MR. MURPHY: Move to strike. Can you answer my question?

MR. SLATER: Wait.

MR. MURPHY: It was nonresponsive.

MR. SLATER: That was directly responsive and maybe you're not understanding, but I object to you -- I think it's argumentative at this point.

MR. MURPHY: What's argumentative?

MR. SLATER: Claiming that he wasn't responsive.

MR. MURPHY: I simply moved to strike as not responsive. That's all. There's nothing

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argumentative about what I said or how I said it.

MR. SLATER: I think it is, because it's like the third time now he's explaining in very clear terms his answer, which is denying the premise of your question in very direct and clear terms.

MR. MURPHY: Adam, don't testify.

MR. SLATER: Trust me, do you think he needs me to testify?

MR. MURPHY: No, he does not. That's the point.

MR. SLATER: I'm not testifying. I'm just trying to get him to dinner, although I guess it doesn't matter what happens. The time runs no matter what so...

BY MR. MURPHY:

Q. There were, Doctor, two studies conducted at Columbia University that were the subject of papers in which

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you were involved; correct?

MR. SLATER: Objection; lack of foundation.

You can answer.

THE WITNESS: I've published far more than two papers in my career at Columbia University.

MR. MURPHY: Regarding olmesartan. I'm sorry --

MR. SLATER: Objection; lack of foundation.

You can answer.

THE WITNESS: I would have to count. I believe it was more. I can go through it, if you'd like, and tell me which ones --

MR. MURPHY: No. I will ask you a better question. It was a poorly phrased question.

BY MR. MURPHY:

Q. You mentioned the Greywoode paper. Were you an author on the Greywoode paper?

A. Yes.

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Q. And then there was a 2015 Lagana paper. Were you an author on that paper?

A. Can you specify which one? He's authored a few papers, some of which might have more than one in 2015?

Q. Sure.

MR. SLATER: Is that the abdominal pain paper, words in the title "abdominal pain"?

MR. MURPHY: "Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers."

THE WITNESS: Yes, I was an author of that paper.

MR. MURPHY: Okay.

BY MR. MURPHY:

Q. So with regard to the Greywoode paper and the Lagana paper of 2015 that I just identified for you, did either of those papers show an association between olmesartan use and